Supplemental Table 1

Research Gaps(RGs)	Research Recommendations(RRs)
RG 1: A need for realistic *in silico*, *in vitro*, and *in vivo* models that more precisely recapitulate the tumour and its micro/macro-environment, to enable comprehensive dissection of the relevant mechanisms governing the transition from normal colorectum to the different malignant stages of the disease	RR1.1: Develop and share appropriate model systems that mimic different pre-malignant/malignant stages of colorectal cancer(CRC), to ensure discovery research questions are addressed in the relevant genetic/clinical context
	RR1.2: Comprehensively interrogate the normal and APC-mutant colorectal crypt to reveal differences that may be exploitable for CRC prevention/control
	RR1.3: Better understand the molecular/cellular interplay between the CRC tumour and its microenvironment
	RR1.4: Determine the role of the gut microbiome and how it can be exploited to improve CRC disease outcomes
RG2: Insufficient evidence on the precise contributions of genetic, environmental and lifestyle factors, and in particular how they interact together to influence the risk of developing CRC.	RR2.1: Conduct comprehensive genetic susceptibility studies, supported by enabling data-sharing platforms, in appropriately diverse human populations to maximise identification of genetic risks factors that have general applicability, or are relevant to specific ethnic populations
	RR2.2: Develop robust data analytical tools that define and quantify the precise interplay between genetic and environmental/lifestyle factors to attributable CRC risk

	RR2.3: Design and implement prospective high quality pan-population studies of risk factors for CRC, with robust clinical/pathological data, supporting blood and tissue samples, to inform a population-based assessment of risk
RG3: A need for intervention trials of preventive strategies addressing 'dose', timing, target group and acceptability, as well as mechanism of action	RR3.1: Encourage trans-disciplinary, multi-modal approaches to CRC prevention, through cross-community collaboration
	RR3.2: Ensure future delivery of high-quality robust long-term studies that identify the appropriate level of intervention including dose, duration, timing, feasibility, acceptability as well as clinically-relevant outcome(s)
RG4: Lack of interdisciplinary collaboration is undermining evaluation of real life preventative interventions in CRC	RR4.1: Coordinate interventional trial activity to ensure maximum impact of precise and effective prevention strategies across the population
	RR4.2: Promote studies that help elucidate mechanism-of-action of prevention interventions
	RR4.3: Develop precise individual risk-stratification approaches to ensure prevention interventions are employed most effectively.
RG5: Lack of an optimal strategy for screening for CRC	RR5.1: Embed research RCTs in FIT-based screening programmes to explore the optimal FIT threshold and/or the role of Flexible Sigmoidoscopy, incorporating risk adjustment algorithms.
RG6: Lack of an effective triage system for symptomatic patients that can determine who will benefit most from invasive investigation	RR6.1: Establish accurate risk-based assessment of symptomatic patients, incorporating FIT and promising novel technologies
	RR6. 2: Develop and trial sensitive and specific tests that could be employed in both screening and symptomatic services.
RG7: Imprecise pathological assessment of CRC is an unmet challenge	RR7.1: Precisely define the morpho-molecular taxonomy of precursor lesions and early-stage disease to help inform risk-stratification in CRC

	RR7.2: Develop new standardised molecularly-informed multi-parameter algorithms to permit improved prediction of disease recurrence and therapy response
	RR7.3: Use our evolving understanding of the CRC tumour and its microenvironment to underpin standardised approaches for pathology specimen analysis
RG8: Lack of qualified personnel to apply state-of-the-art knowledge in genomics, big data science and digital pathology	RR8.1: Embed interdisciplinary education/training within undergraduate/ postgraduate and continuing professional education curriculae to ensure recruitment, retention and upskilling of qualified personnel to deliver modern pathology to the CRC community
RG9: Inadequate assessment and communication of risk, benefit and uncertainty of treatment choices where cure is possible	RR9.1: Develop an appropriate evidence base to inform shared decision-making for potentially curative therapies for patients.
RG10: A need for novel technologies/interventions that have the potential to improve curative outcomes.	RR10.1: Establish optimum peri-therapeutic interventions to improve curative outcomes
	RR10.2: Optimise curative approaches for metastatic or recurrent disease, that balance patients expectations with treatment efficacy and health-preserving benefit
	RR10.3: Develop biomarkers that define the optimal curative therapeutic strategy for an individual or group, preventing over-treatment and improving treatment selection
	RR10.4: Develop research methodologies to optimally evaluate new curative approaches

RG11: Lack of approaches that take cognisance of the molecular interplay between the metastasising tumour and its microenvironment and help guide evolution of innovative treatments that deliver improved health outcomes for the Stage IV patient	RR11.1: Develop evidence-based approaches utilising multi-modality treatment for patients with stage IV CRC to maximise the utility of cutting-edge technologies to improve outcomes.
RG12: Lack of reliable prognostic and predictive biomarkers to help guide stage IV patient pathways	RR12.1: Establish robust prognostic and predictive biomarkers to stratify patients to ensure every patient receives “bespoke” treatment, relevant to their particular disease course
	RR12.2: Employ our evolving understanding of the role of the tumour microenvironment in CRC to develop innovative therapies that modulate the microenvironment for clinical benefit
RG13: The need to increase understanding of Health-Related-Quality-of-Life(HRQOL) issues and promote their resolution as part of a research effort to enhance survivorship for those living with and beyond CRC	RR13.1: Precisely characterise the landscape of HRQOL sequelae in patients living with and beyond CRC, including those in receipt of novel treatment approaches (e.g. immunotherapy)
	RR13.2: Elucidate the causes of symptoms following CRC treatment and develop viable solutions for their prevention and/or management
	RR13.3: Evaluate the evidence base and impact of lifestyle interventions, including increased physical activity and better nutrition, in CRC
	RR13.4: Develop research to support survivorship care planning and promote shared decision-making for people living with and beyond CRC

RG14: Lack of coordination of CRC research and its funding, leading to fragmented efforts to elucidate the biology of the disease and translate this knowledge into new preventative agents, screening tools, diagnostics and therapeutics	RR14.1: Establish an annual national multi-disciplinary CRC research conference, that draws together the entire CRC community in a co-ordinated research effort
	RR14.2 Develop bespoke data-analytics platforms that maximise the value of CRC genomic, clinical, epidemiological and lifestyle data
	RR14.3: Prioritise research resource allocation to recognised research gaps and encourage collaborative research grant calls between complimentary research funding organisations
RG15: Lack of effective communication strategies between Health Care Professions, CRC patients/survivors, those at elevated risk of developing CRC, and the general public and varying levels of awareness of key risk factors, prevention options and benefits/risks associated with different treatment options	RR15.1: Development of patient- and person-adapted educational materials and shared decision-making tools, in order to empower individual choice
	RR15.2: Embedding strategies that ensure appropriate communication of risk and benefit and best capture Patient Reported Outcome Measures(PROMS) in order to ensure optimal outcomes for patients, their families and carers and those at-risk of developing CRC

Supplemental Table 1 Critical Research Gaps and Research Recommendations